a) contacting a sample of intestinal tissue which includes the basement membrane of the laminapropria with fully-complementary, detectable oligonucleotide probes that hybridize to mRNA that encodes ST receptor protein for a time sufficient for said fully-complementary, detectable oligonucleotide probes to hybridize to mRNA that encodes ST receptor protein present in cells of said sample;

b) removing detectable oligonucleotide probes which are not hybridized to mRNA that encodes ST receptor protein in cells of said sample; and

c) examining said sample to detect the presence of detectable oligonucleotide probes hybridized to mRNA that encodes ST receptor protein present in cells in the basement membrane of the laminapropria;

wherein the presence of mRNA that encodes ST receptor protein in cells in the basement membrane of the laminapropria indicates invasion of neoplastic colorectal cells into the basement membrane of the laminapropria of an individual.

REMARKS

Claims 9 to 26 are pending in the present application. No new claims have been added, claims 9 to 22 have been cancelled as drawn to non-elected inventions, and claims 23 and 25 have been amended herein. Upon entry of the amendments, claims 23 to 26 will remain pending. Support for the amendments in found in the specification, at, for example, page 33, line 3 to page 34, line 19. As the amendments remove issues for appeal, Applicant respectfully requests entry thereof. MPEP § 714.13.

I. The Specification Fully Enables Practice of the Claimed Methods

Claims 23 to 26 stand rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. Applicant respectfully traverses the rejection because the specification, coupled with the knowledge of one of ordinary skill in the art at the time of filing, enable the skilled artisan to make and use the full scope of the subject matter defined by the present claims without undue experimentation.

The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance. *In re Marzocchi*, 169 U.S.P.Q. 152 (C.C.P.A. 1975). Patents and other publications that predate a pending application may be offered to prove the state of the art for purposes of establishing enablement. *In re Budnick*, 537 F.2d 535, 538, 190 U.S.P.Q. 536, 543 (C.C.P.A. 1976); *In re Glass*, 492 F.2d 1228, 1232, 181 U.S.P.Q. 31, 34 (C.C.P.A. 1974).

The specification teaches the skilled artisan how to design fully-complementary probes that selectively hybridize to human mRNA encoding the ST receptor protein utilizing the sequence information provided in *Sauvage et al., J. Biol. Chem.* 266, 1991, 17912-17918, and further teaches the skilled artisan how to use the probes in *in situ* methods to detect the invasion of neoplastic colorectal cells into the basement membrane of the laminapropria. *See* page 33, line 3 to page 34, line 19. In addition, methods for performing *in situ* hybridization experiments under conditions in which oligonucleotide probes hybridize to target mRNA and do not hybridize to similar, non-target mRNA were within the expertise of one of ordinary skill in the art at the time of filing. DeLellis,

R.A., *Human Pathology*, 25, **1994**, 580-585 (hereinafter "the DeLellis reference"), attached hereto as Appendix A. For example, the DeLellis reference explains that:

> oligonucleotide sequences can be constructed from published cDNA maps...A major advantage of these probes is that they can be used to achieve high levels of specificity under conditions of high stringency [in *in situ* hybridization (ISH) experiments]. Moreover, it is possible to generate discriminating sequences for similar genes and to construct different probes for a particular sequence in order to prove [*sic*: improve] hybridization specificity. In studies of monoclonal B-cell lines with immunoglobulin variable region (VH) genes of known nucleic acid sequence, Long et al showed high levels of specificity for 35S labeled oligonucleotide probes. Clones expressing more than 90 % sequence homology could be distinguished using ISH.

Id. at 581. Based upon the state of the art at the time of filing, the specification would have enabled the skilled artisan to design fully-complementary oligonucleotide probes that would hybridize to mRNA encoding the ST receptor protein during *in situ* hybridization and would not hybridize to similar mRNA sequences. The specification thus enables the skilled artisan to make and use the full scope of the subject matter defined by the present claims without undue experimentation.

The Office Action asserts that "the claims should specify the chemical nature of the probes to be used in the claimed methods, because clearly Schulz demonstrates that sequences similar to ST receptor coding sequences are detectable." (Office Action dated October 23, 2001, page 3.) Claims 23 and 25 have been amended to specify that the oligonucleotide probes used in the *in situ* methods of the invention are fully-complementary to the target mRNA sequences that encode the ST receptor protein. The oliogonucleotide probes defined in claims 23 and 25 therefore possess nucleotide sequences that are the exact complement of the nucleotide sequence of mRNA encoding the ST receptor protein, and their chemical nature has thus been specified.

Moreover, as discussed above, it was well within the expertise of one of ordinary skill in the art at the time of filing to perform *in situ* hybridization experiments under conditions in which fully complementary oligonucleotide probes would hybridize to target mRNA and would not hybridize to similar, non-target mRNA. The specification, coupled with the expertise of one of ordinary skill in the art, therefore enabled the skilled artisan to perform *in situ* hybridization experiments without undue experimentation under conditions in which fully complementary oligonucleotide probes would hybridize to mRNA that encodes ST receptor protein and would not hybridize to mRNA sequences that are similar to ST receptor coding sequences. Applicant respectfully submits that the specification enables the full scope of the subject matter defined by the present claims and, accordingly, requests withdrawal of the rejection.

II. Alleged Double Patenting

Claims 23 to 26 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims one and four of U.S. Patent No. 5,601,990. Applicant requests that this rejection be deferred pending some identification of allowable subject matter, as it likely can be readily resolved (depending upon the subject matter ultimately allowed) through the filing of a suitable terminal disclaimer. If the Examiner determines that the claims as amended are allowable, Applicant invites the Examiner to telephone Applicant's undersigned representative who will telefax a suitable terminal disclaimer to the Examiner to facilitate advancement of the application to issue.

III. Conclusion

In view of the foregoing, Applicant submits that the claims are in condition for allowance, and an early Office Action to that effect is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Respectfully submitted,

Date: December 11, 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Please cancel claims 9 to 22.

Please amend claims 23 and 25 as follows.

23. (Twice Amended) An in situ method of detecting invasion of neoplastic colorectal cells into the basement membrane of the laminapropria of a human comprising the steps of:

a) obtaining a sample of intestinal tissue which includes the basement membrane of the laminapropria;

b) contacting said sample with fully-complementary, detectable oligonucleotide probes that hybridize to mRNA that encodes ST receptor protein for a time sufficient for said fully-complementary, detectable oligonucleotide probes to hybridize to mRNA that encodes ST receptor protein present in cells of said sample;

c) removing detectable oligonucleotide probes which are not hybridized to mRNA that encodes ST receptor protein in cells of said sample; and

d) examining said sample to detect the presence of detectable oligonucleotide probes hybridized to mRNA that encodes ST receptor protein present in cells in the basement membrane of the laminapropria;

wherein the presence of mRNA that encodes ST receptor protein in cells in the basement membrane of the laminapropria indicates invasion of neoplastic colorectal cells into the basement membrane of the laminapropria of an individual.

25. (Twice Amended) An in situ method of detecting invasion of neoplastic colorectal cells into the basement membrane of the laminapropria of a human comprising the steps of:

a) contacting a sample of intestinal tissue which includes the basement membrane of the laminapropria with fully-complementary, detectable oligonucleotide probes that hybridize to mRNA that encodes ST receptor protein for a time sufficient for said fully-complementary, detectable oligonucleotide probes to hybridize to mRNA that encodes ST receptor protein present in cells of said sample;

b) removing detectable oligonucleotide probes which are not hybridized to mRNA that encodes ST receptor protein in cells of said sample; and

c) examining said sample to detect the presence of detectable oligonucleotide probes hybridized to mRNA that encodes ST receptor protein present in cells in the basement membrane of the laminapropria;

wherein the presence of mRNA that encodes ST receptor protein in cells in the basement membrane of the laminapropria indicates invasion of neoplastic colorectal cells into the basement membrane of the laminapropria of an individual.